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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/733,692	12/08/2000	Brian R. Murphy	15280404100	3239

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NATIONAL INSTITUTES OF HEALTH
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EXAMINER
CHEN, STACY BROWN

ART UNIT	PAPER NUMBER
1648	

DATE MAILED: 04/18/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/733,692	MURPHY ET AL.	
	Examiner	Art Unit	
	Stacy B. Chen	1648	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *15 February 2006*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *180-222* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *180-222* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *08 December 2002* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. Applicant's amendment filed February 15, 2006 is acknowledged and entered. Claims 180-222 are pending and under examination.

2. The rejection of claims 180-222 under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention, is withdrawn in view of Applicant's amendment. The claims recited, "attenuated for replication at least 10-fold in the respiratory tract of a primate host infected with said chimeric PIV". This limitation was deemed unclear because it lacked comparative basis for the term "10-fold". Applicant's amendment to include a comparative basis for "10-fold" overcomes this rejection.

Claim Rejections - 35 USC § 112

3. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 190-195 and 213-217 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. The claims are drawn to chimeric viruses, specifically wherein the substitution mutation at position 456 of the L protein is "to another amino acid". The breadth of

the claims has not been adequately described such that one of skill in the art would know how to practice the invention.

Applicant's arguments have been carefully considered but fail to persuade. Applicant argues that the Federal Circuit states that a sequence need not appear in a patent specification to support a DNA-based invention provided that the state of the scientific knowledge at the time the application was filed includes such structural information. Applicant cites *Capon et al. v. Eshhar et al. v. Dudas*, 76 USPQ2d 1078 (Fed. Cir. 2005). Applicant argues that the skilled artisan would be fully aware of the structure of the genus of polypeptides claimed. Applicant asserts that the skilled artisan would merely have to replace the nucleotide sequence encoding an amino acid at the specific location recited in the claims with any of the well-known nucleotide sequences that encode the desired amino acid.

In response to Applicant's arguments, the examiner has considered *Capon et al. v. Eshhar et al. v. Dudas*, 76 USPQ2d 1078 (Fed. Cir. 2005). Capon *et al.* and Eshhar *et al.* disclosed the sequences of those that were to be recombined. The Fed Circuit noted in section [1], that "since written description requirement must be applied in context of particular invention and state of knowledge, and there is no per se rule that nucleotide sequence must be recited anew when that information is already known in art, since invention at issue lies not in discovering which DNA segments are related to immune response, but in novel combination of segments to achieve novel result, since claimed chimeric genes are prepared from known DNA sequence of known function, and since requirement that these sequences be analyzed and reported in specifications therefore does not add descriptive substance."

In this case, Applicant has provided a base structure in which the nucleotides encoding an amino acid are to be substituted for the naturally occurring nucleotides encoding a different amino acid. In *Capon et al. v. Eshhar et al. v. Dudas*, the sequences to be combined were provided in full. Applicant has provided the nucleotides to be substituted into the base structure, and points to the known nucleotides that are available which encode amino acids. The Office assumes that Applicant is referring to at least the 60 codons that encode the 20 common amino acids: gca, gcc, gcg, gcu, ugc, ugu, gac, gau, gaa, gag, uuc, uuu, gga, ggc, ggg, ggu, cac, cau, aua, auc, auu, aaa, aag, uua, uug, cua, cuc, cug, cuu, aug, aac, aau, cca, ccc, ccg, ccu, caa, cag, aga, agg, cga, cgc, cgg, cgu, agc, agu, uca, ucc, ucg, ucu, aca, acc, acg, acu, gua, guc, gug, guu, ugg, uac and uau.

While the sequences are provided in full, as in *Capon et al. v. Eshhar et al. v. Dudas,* the function of the substituted codon is not known. In *Capon et al. v. Eshhar et al. v. Dudas*, the invention of Capon does not concern the discovery of gene function or structure, but are prepared from known DNA sequences of known function. On this point, *Capon et al. v. Eshhar et al. v. Dudas*, and the instant application differ.

In this case, the function of the codons in the base structure is not known. Applicant has failed to provide a structure/function nexus between the substituted codon (structure) and its desired function (attenuation). For Applicant to claim a genus of substitutions for which Applicant has not given a starting point, one of skill in the art would need to discover which of gca, gcc, gcg, gcu, ugc, ugu, gac, gau, gaa, gag, uuc, uuu, gga, ggc, ggg, ggu, cac, cau, aua, auc, auu, aaa, aag, uua, uug, cua, cuc, cug, cuu, aug, aac, aau, cca, ccc, ccg, ccu, caa, cag, aga, agg, cga, cgc, cgg, cgu, agc, agu, uca, ucc, ucg, ucu, aca, acc, acg, acu, gua, guc, gug, guu, ugg, uac

and uau, is an attenuating mutation. In other words, if Applicant had provided a nexus, such as hydrophilic amino acids can be substituted for position 456 of the L protein, one of skill in the are would be have a connection between the substitution and the function of attenuation. Applicant has not provided this. Therefore, the claims remain rejected for reasons of record.

Claim Rejections - 35 USC § 102

4. The rejection of claims 180-189, 196-212 and 218-220 as being anticipated by Belshe *et al.* (US 5,869,036, "Belshe"), is withdrawn in view of Applicant's persuasive arguments.

With regard to the claims that recite, "said partial or complete PIV genome or antigenome comprising a polynucleotide encoding a wild-type L protein of the PIV", the limitation distinguishes the claims from Belshe. Applicant argues, and the examiner agrees that Example 5 is directed to a complementation assay, wherein the L gene (among others) was introduced into a plasmid. CV-1 cells were co-transfected with the plasmid vector pRSV-T and one or more recombinant plasmids, such as the L gene. Twenty-four hours post-transfection, the expressing cells were infected with cp45 virus. Based on this complementation assay, Belshe concludes that cp45 viruses complemented with the wild-type L protein, produced by the cell, are capable of replicating at the non-permissive temperature for the cp45 virus (col. 16, lines 54-62). The wild-type L gene is not incorporated into the genome (as required by the claims). Therefore, Belshe does not teach or suggest the invention as claimed in claims 180, 184, 200, 201, 202, 203, 205, 208, 210 and 219.

With regard to the claims that specify the type of insertion into the PIV genome, the limitation distinguished over Belshe. Applicant argues, and the examiner agrees that Belshe

discloses hybrid genomes that are derived by substituting the regions encoding F and HN proteins of cp45 with cDNA copies of corresponding genes of a target virus (Belshe, col. 9, lines 54-59 and col. 10, lines 19-22). Applicant argues that the substation replaces the gene segment normally present at the same location, not between two open reading frames within or encompassing an ORF. Claim 181, for example, recites, "said heterologous gene(s) or genome segment(s) being inserted into the PIV genome or antigenome at one or more site(s) selected from the group consisting of a site between the P and M open reading frames, a site between the N and P open reading frames, a site between the HN and L open reading frames and a site between the 3' leader and the N open reading frame." Belshe does not teach or suggest insertion of heterologous genes between open reading frames, rather, replacing native reading frames with heterologous ones (substitution).

Lastly, with regard to the claims that recite, "wherein said heterologous genome segments are operatively linked to a gene start sequence and to a gene end sequence of said PIV", Applicant argues, and the examiner agrees that Belshe does not teach this limitation. Therefore, the rejection of claims 180-189, 196-212 and 218-220 is withdrawn.

Claim Rejections - 35 USC § 103

5. Claims 196, 198, 200, 201, 202, 218, 220, and 222 are rejected under 35 U.S.C. 103(a) as being unpatentable over Belshe. (Note that claim 202 is included in this rejection, as it depends from claim 200. The inclusion of claim 202 in this rejection is not expected to alter the rejection because it is drawn to an immunogenic composition comprises the active ingredient of claim

200, from which is depends.) The rejection of claims 197, 199, 219 and 221 is withdrawn in view of Applicant's persuasive arguments.

Claims 197, 199, 219 and 221 recite, "said partial or complete PIV genome or antigenome comprising a polynucleotide encoding a wild-type L protein of the PIV", the limitation distinguishes the claims from Belshe. Applicant argues, and the examiner agrees that Example 5 is directed to a complementation assay, wherein the L gene (among others) was introduced into a plasmid. CV-1 cells were co-transfected with the plasmid vector pRSV-T and one or more recombinant plasmids, such as the L gene. Twenty-four hours post-transfection, the expressing cells were infected with cp45 virus. Based on this complementation assay, Belshe concludes that cp45 viruses complemented with the wild-type L protein, produced by the cell, are capable of replicating at the non-permissive temperature for the cp45 virus (col. 16, lines 54-62). The wild-type L gene is not incorporated into the genome (as required by the claims).

However, claims 196, 198, 200, 201, 202, 218, 220, and 222 remain rejected under 35 U.S.C. 103(a) as being unpatentable over Belshe. The claims are drawn to embodiments described above, wherein the heterologous gene segments are inserted operatively linked to a gene start and a gene end sequence of the PIV background genome. This limitation does not lend patentability to the claimed invention because insertion of heterologous gene encoding the antigenic determinant would only be appropriate between a gene start and gene end sequence. One would have been motivated to use the gene start and gene end sequences of Belshe's background PIV in order to retain as much stability as possible when expressing the heterologous genes. One would have had a reasonable expectation of success given the fundamental nature of

recombination and the desire to obtain stable expression. Therefore, the claimed subject matter would have been obvious to one of ordinary skill in the art at the time the invention was made.

Applicant argues that Belshe only discloses that the "gene sequence which encodes [the desired protein]...may be substituted for the corresponding sequence in the cp45 genome", (Belshe, col. 8, lines 59-61). Applicant points to Belshe's Figure 1, which does not depict any non-translated, intergenic sequences. Applicant argues that the Office's analysis of obviousness relies on improper hindsight.

In response to Applicant's argument that the examiner's conclusion of obviousness is based upon improper hindsight reasoning, it must be recognized that any judgment on obviousness is in a sense necessarily a reconstruction based upon hindsight reasoning. But so long as it takes into account only knowledge which was within the level of ordinary skill at the time the claimed invention was made, and does not include knowledge gleaned only from the applicant's disclosure, such a reconstruction is proper. See *In re McLaughlin*, 443 F.2d 1392, 170 USPQ 209 (CCPA 1971).

In this case, one would have been motivated to use the gene start and gene end sequences of Belshe's background PIV in order to retain as much stability as possible when expressing the heterologous genes. Belshe teaches that "the region of the genome of the target virus that encodes one or more surface glycoproteins may be combined with the regions of the cp45 genome related to replication and internal structure of the virus", see col. 8, lines 59-66. As for Figure 1, it is a schematic representation of the HPIV-3 viral genome with the attenuation mutations (cp45). Figure 1 does not appear to indicate anything about inserting heterologous sequences, and thus is not relevant to insertion of heterologous genes. One would have had a

reasonable expectation of success given the fundamental nature of recombination and the desire to obtain stable expression. Securing stable expression is not a concept from Belshe, rather, from the knowledge of one or ordinary skill in the art generally relating to recombination and heterologous gene expression. Therefore, the rejection is maintained for reasons of record.

Double Patenting

6. Claims 180-222 remain provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 144-215 of copending Application No. 09/083,793, for reasons of record. Although the conflicting claims are not identical, they are not patentably distinct from each other because the subject matter of the copending application is encompasses the embodiments set forth in the instant claims. This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

7. Claims 180-222 remain provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 53-85 of copending Application No. 09/458,813, for reasons of record. Although the conflicting claims are not identical, they are not patentably distinct from each other because the subject matter of the copending application is encompasses the embodiments set forth in the instant claims. This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

8. Claims 180-222 remain provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-30 and 46-74 of copending

Application No. 09/459,062, for reasons of record. Although the conflicting claims are not identical, they are not patentably distinct from each other because the subject matter of the copending application is encompasses the embodiments set forth in the instant claims. This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

9. Claims 180-222 remain provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 84-163 of copending Application No. 09/586,479, for reasons of record. Although the conflicting claims are not identical, they are not patentably distinct from each other because the subject matter of the copending application is a species of the instantly claimed genus of PIVs, rendering the genus claims obvious. This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Conclusion

10. No claim is allowed.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period

will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Stacy B. Chen whose telephone number is 571-272-0896. The examiner can normally be reached on M-F (7:00-4:30). If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James C. Housel can be reached on 571-272-0902. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Stacy B. Chen 4/17/2006
Stacy B. Chen
Primary Examiner
April 17, 2006